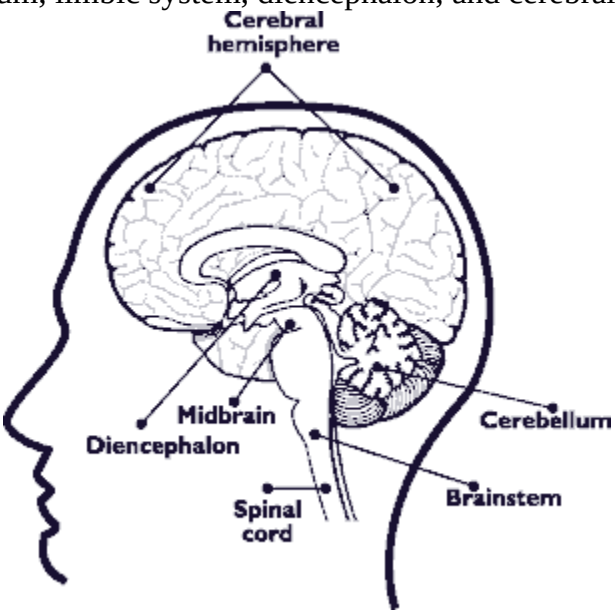
Introduction and Background

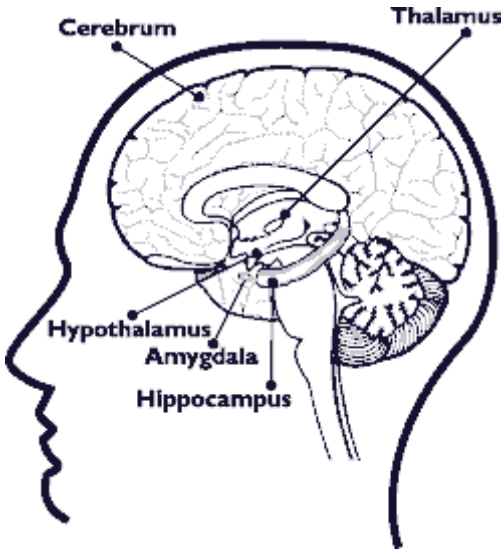
The brain consists of several large regions, each responsible for some of the activities vital for living. These include the brainstem, cerebellum, limbic system, diencephalon, and cerebral cortex.



The brainstem is the part of the brain that connects the brain and the spinal cord. It controls many basic functions, such as heart rate, breathing, eating, and sleeping. The brainstem accomplishes this by directing the spinal cord, other parts of the brain, and the body to do what is necessary to maintain these basic functions.

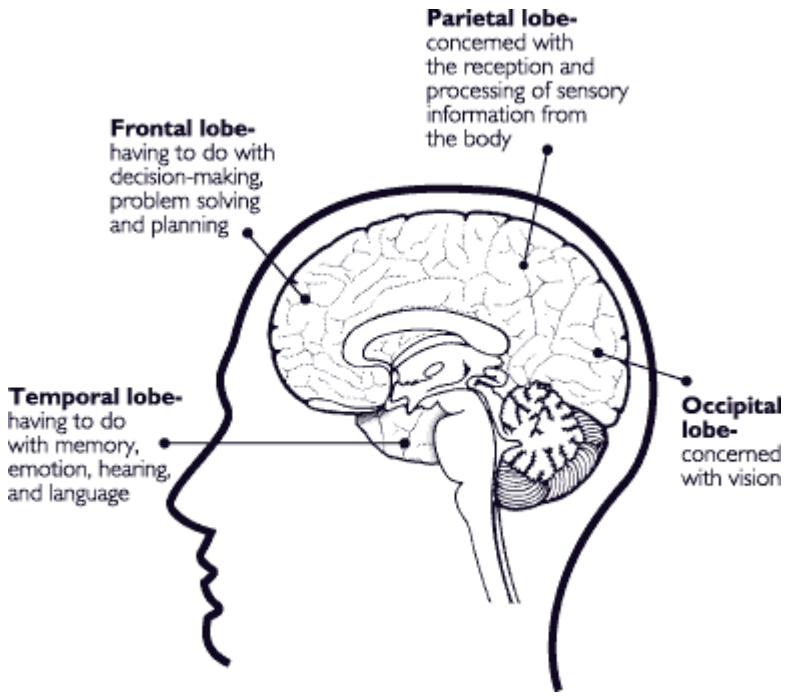
The cerebellum, which represents only one-eighth of the total weight of the brain, coordinates the brain's instructions for skilled repetitive movements and for maintaining balance and posture. It is a prominent structure located above the brainstem.

On top of the brainstem and buried under the cortex, there is a set of more evolutionarily primitive brain structures called the limbic system. The limbic system structures are involved in many of our emotions and motivations, particularly those that are related to survival, such as fear, anger, and emotions related to sexual behavior. The limbic system is also involved in feelings of pleasure that are related to our survival, such as those experienced from eating and sex. Two large limbic system structures called the amygdala and hippocampus are also involved in memory. One of the reasons that drugs of abuse can exert such powerful control over our behavior is that they act directly on the more evolutionarily primitive brainstem and limbic structures, which can override the cortex in controlling our behavior. In effect, they eliminate the most human part of our brain from its role in controlling our behavior.



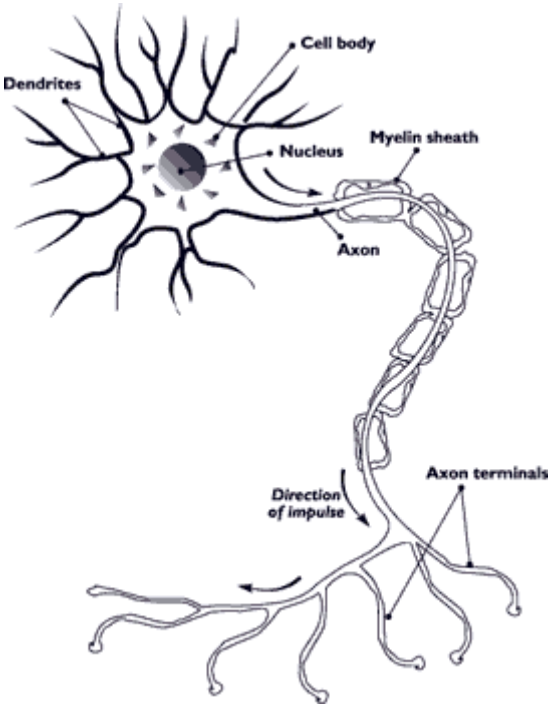
The diencephalon, which is also located beneath the cerebral hemispheres, contains the thalamus and hypothalamus. The thalamus is involved in sensory perception and regulation of motor functions (i.e., movement). It connects areas of the cerebral cortex that are involved in sensory perception and movement with other parts of the brain and spinal cord that also have a role in sensation and movement. The hypothalamus is a very small but important component of the diencephalon. It plays a major role in regulating hormones, the pituitary gland, body temperature, the adrenal glands, and many other vital activities.

The cerebral cortex, which is divided into right and left hemispheres, encompasses about two-thirds of the brain mass and lies over and around most of the remaining structures of the brain. It is the most highly developed part of the human brain and is responsible for thinking, perceiving, and producing and understanding language. It is also the most recent structure in the history of brain evolution. The cerebral cortex can be divided into areas that each have a specific function. For example, there are specific areas involved in vision, hearing, touch, movement, and smell. Other areas are critical for thinking and reasoning. Although many functions, such as touch, are found in both the right and left cerebral hemispheres, some functions are found in only one cerebral hemisphere. For example, in most people, language abilities are found in the left hemisphere.



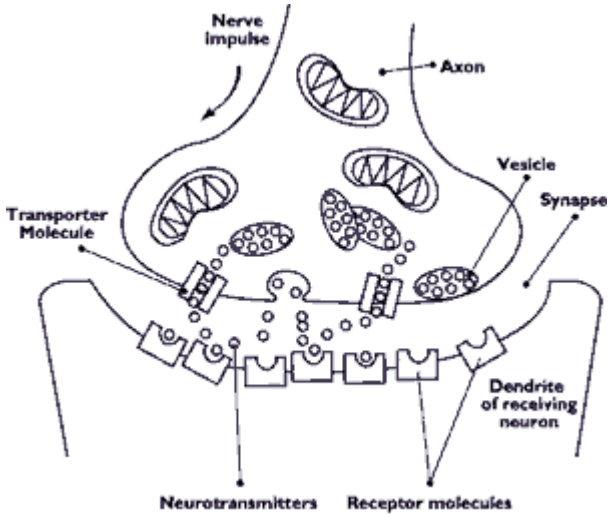
Nerve Cells and Neurotransmission

The brain is made up of billions of nerve cells. Typically, a neuron contains three important parts: a central cell body that directs all activities of the neuron; dendrites, short fibers that receive messages from other neurons and relay them to the cell body; and an axon, a long single fiber that transmits messages from the cell body to the dendrites of other neurons or to body tissues, such as muscles. Although most neurons contain all of the three parts, there is a wide range of diversity in the shapes and sizes of neurons as well as their axons and dendrites.



The transfer of a message from the axon of one nerve cell to the dendrites of another is known as neurotransmission. Although axons and dendrites are located extremely close to each other, the transmission of a message from an axon to a dendrite does not occur through direct contact. Instead, communication between nerve cells occurs mainly through the release of chemical substances into the

space between the axon and dendrites. This space is known as the synapse. When neurons communicate, a message, traveling as an electrical impulse, moves down an axon and toward the synapse. There it triggers the release of molecules called neurotransmitters from the axon into the synapse. The neurotransmitters then diffuse across the synapse and bind to special molecules, called receptors, that are located within the cell membranes of the dendrites of the adjacent nerve cell. This, in turn, stimulates or inhibits an electrical response in the receiving neuron's dendrites. Thus, the neurotransmitters act as chemical messengers, carrying information from one neuron to another.



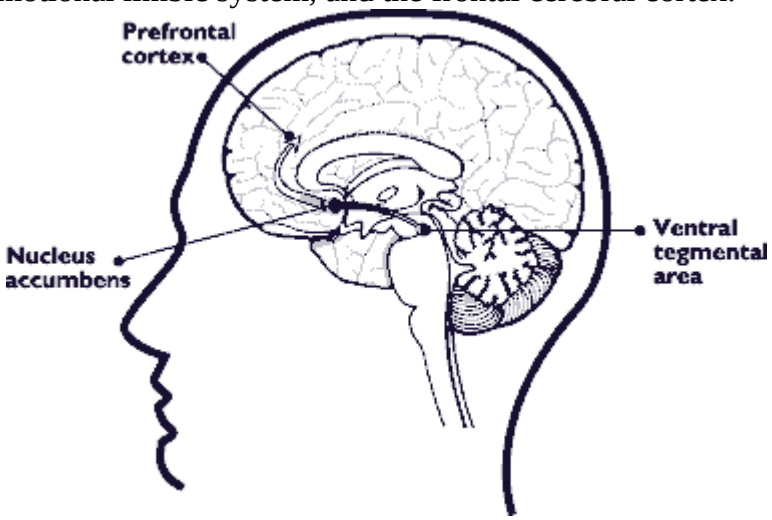
There are many different types of neurotransmitters, each of which has a precise role to play in the functioning of the brain. Generally, each neurotransmitter can only bind to a very specific matching receptor. Therefore, when a neurotransmitter couples to a receptor, it is like fitting a key into a lock. This coupling then starts a whole cascade of events at both the surface of the dendrite of the receiving nerve cell and inside the cell. In this manner, the message carried by the neurotransmitter is received and processed by the receiving nerve cell. Once this has occurred, the neurotransmitter is inactivated in one of two ways. It is either broken down by an enzyme or reabsorbed back into the nerve cell that released it. The reabsorption (also known as re-uptake) is accomplished by what are known as transporter molecules. Transporter molecules reside in the cell membranes of the axons that release the neurotransmitters. They pick up specific neurotransmitters from the synapse and carry them back across the cell membrane and into the axon. The neurotransmitters are then available for reuse at a later time.

As noted above, messages that are received by dendrites are relayed to the cell body and then to the axon. The axons then transmit the messages, which are in the form of electrical impulses, to other neurons or body tissues. The axons of many neurons are covered in a fatty substance known as myelin. Myelin has several functions. One of its most important is to increase the rate at which nerve impulses travel along the axon. The rate of conduction of a nerve impulse along a heavily myelinated axon can be as fast as 120 meters/second. In contrast, a nerve impulse can travel no faster than about 2 meters/second along an axon without myelin. The thickness of the myelin covering on an axon is closely linked to the function of that axon. For example, axons that travel a long distance, such as those that extend from the spinal cord to the foot, generally contain a thick myelin covering to facilitate faster transmission of the nerve impulse.

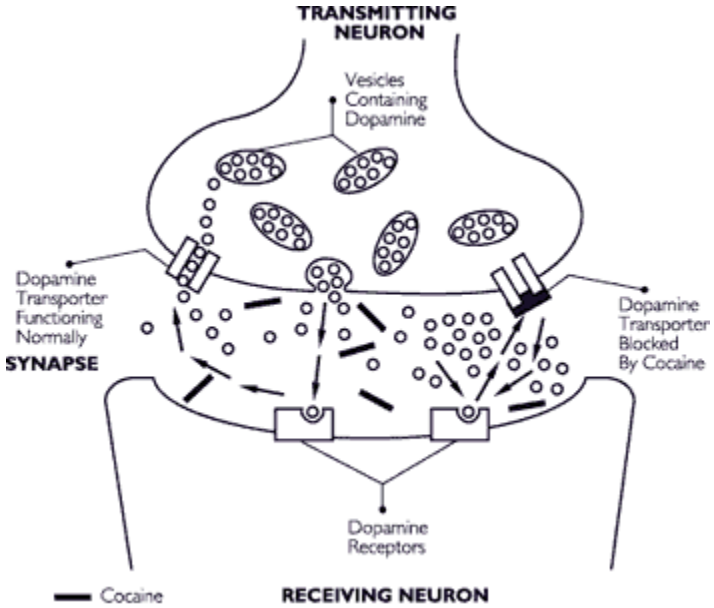
Effects of Drugs of Abuse on the Brain

Pleasure, which scientists call reward, is a very powerful biological force for our survival. If you do something pleasurable, the brain is wired in such a way that you tend to do it again. Life-sustaining activities, such as eating, activate a circuit of specialized nerve cells devoted to producing and regulating pleasure. One important set of these nerve cells, which uses a chemical neurotransmitter called dopamine, sits at the very top of the brainstem in the ventral tegmental area (VTA). These dopamine-containing

neurons relay messages about pleasure through their nerve fibers to nerve cells in a limbic system structure called the nucleus accumbens. Still other fibers reach to a related part of the frontal region of the cerebral cortex. So, the pleasure circuit, which is known as the mesolimbic dopamine system, spans the survival-oriented brainstem, the emotional limbic system, and the frontal cerebral cortex.



All drugs that are addicting can activate the brain's pleasure circuit. Drug addiction is a biological, pathological process that alters the way in which the pleasure center, as well as other parts of the brain, functions. To understand this process, it is necessary to examine the effects of drugs on neurotransmission. Almost all drugs that change the way the brain works do so by affecting chemical neurotransmission. Some drugs, like heroin and LSD, mimic the effects of a natural neurotransmitter. Others, like PCP, block receptors and thereby prevent neuronal messages from getting through. Still others, like cocaine, interfere with the molecules that are responsible for transporting neurotransmitters back into the neurons that released them. Finally, some drugs, such as methamphetamine, act by causing neurotransmitters to be released in greater amounts than normal.



Prolonged drug use changes the brain in fundamental and long-lasting ways. These long-lasting changes are a major component of the addiction itself. It is as though there is a figurative "switch" in the brain that "flips" at some point during an individual's drug use. The point at which this "flip" occurs varies from individual to individual, but the effect of this change is the transformation of a drug abuser to a drug addict.

Alcohol

Upon consumption, alcohol is distributed throughout the water-containing portions of the body, affecting primarily those organs having a high water content. One of these is the liver, which is the organ that metabolizes alcohol. Another is the brain, the organ that is the seat of cognition and behavior.

Alcohol and the brain: For many years, scientists thought that alcohol altered the function of neurons in the brain by interacting with fat molecules in the cell membranes. More recently, it has become apparent that alcohol interacts with proteins found in the cell membranes, particularly those involved in neurotransmission. Like other drugs of addiction, alcohol acts via the brain's reward pathway in the limbic system. However, alcohol is unlike other drugs in that it interacts with multiple systems in the brain, sometimes stimulating and at other times inhibiting neurotransmission.

After drinking a sufficient amount of alcohol, many individuals experience a pleasurable state of mind. This pleasurable sensation leads some individuals to seek repeated exposure to alcohol. If drinking is excessive, it can lead to confusion, loss of coordination, sedation, coma, and even death. Long-term exposure to alcohol can lead to tolerance of its effects and eventually to physical dependence. The term "tolerance" refers to a decrease in brain sensitivity to alcohol following long-term exposure. If alcohol-dependent individuals stop drinking, they experience withdrawal symptoms, which may include tremors, anxiety, sweating, hallucinations, and seizures. The site of action of all these effects is the brain.

The physiological and behavioral changes associated with intoxication reflect the effects of alcohol on various parts of the brain. For example, the loss of coordination observed in intoxicated individuals may result from the effects of alcohol on a portion of the brain called the cerebellum, which functions in the control of movement. Alcohol-induced memory lapses may result from impairment of the hippocampus, a part of the brain that helps store new memories. Drinking can be sufficiently excessive that death results from suppression of the brainstem activity that controls breathing and circulation.

Stimulants

Stimulant drugs such as cocaine, "crack," amphetamines, and caffeine are substances that speed up activity in the brain and spinal cord. This, in turn, can cause the heart to beat faster and blood pressure and metabolism to increase. Stimulants often influence a person to be more talkative and anxious and to experience feelings of exhilaration.

Use of cocaine and other stimulants can cause someone's heart to beat abnormally fast and at an unsteady rate. Use of these drugs also narrows blood vessels, reducing the flow of blood and oxygen to the heart, which results in "starving" the heart muscle. Even professional athletes whose bodies are well-conditioned have succumbed to cocaine's ability to cause heart failure. Researchers currently have no way to detect who may be more susceptible to these effects.

Cocaine acts on the pleasure circuit to prevent reabsorption of the neurotransmitter dopamine after its release from nerve cells. Normally, neurons that are part of the pleasure circuit release dopamine, which then crosses the synapse to stimulate another neuron in the pleasure circuit. Once this has been accomplished, the dopamine is picked up by a transporter molecule and carried back into the original neuron. However, because cocaine binds to the dopamine transporter molecule, it prevents the reabsorption of dopamine. This causes a build up of dopamine in the synapse, which results in strong feelings of pleasure and even euphoria. The excess dopamine that accumulates in the synapse causes the neurons that have dopamine receptors to decrease the number of receptors they make. This is called down regulation. When cocaine is no longer taken and dopamine levels return to their normal (i.e., lower) concentration, the smaller number of dopamine receptors that are available for the neurotransmitter to bind to is insufficient to fully activate nerve cells. This results in a drug "craving," which is a way of telling the addict to get the level of dopamine back up by taking cocaine. Cocaine also binds to the transporters for other neurotransmitters, including serotonin and norepinephrine, and blocks their re-uptake. Scientists are still unsure about the effects of cocaine's interaction with these other neurotransmitters.

Cocaine has also been found to specifically affect the prefrontal cortex and amygdala, which are involved in aspects of memory and learning. The amygdala has been linked to emotional aspects of memory. Researchers believe that a neural network involving these brain regions reacts to environmental cues and activates memories, and this triggers biochemical changes that result in cocaine craving.

Amphetamines, such as methamphetamine, also act on the pleasure circuit by altering the levels of certain neurotransmitters present in the synapse, but the mechanism is different from that of cocaine. Chemically, methamphetamine is closely related to amphetamine, but it has greater effects on the brain. Methamphetamine is also chemically similar to dopamine and another neurotransmitter, norepinephrine. It produces its effects by causing dopamine and norepinephrine to be released into the synapse in several areas of the brain, including the nucleus accumbens, prefrontal cortex, and the striatum, a brain area involved in movement. Specifically, methamphetamine enters nerve terminals by passing directly through nerve cell membranes. It is also carried into the nerve terminals by transporter molecules that normally carry dopamine or norepinephrine from the synapse back into the nerve terminal. Once in the nerve terminal, methamphetamine enters dopamine and norepinephrine containing vesicles and causes the release of these neurotransmitters. Excess dopamine and norepinephrine would normally be chewed up by enzymes in the cell, however, methamphetamine

blocks this breakdown. The excess neurotransmitters are then carried by transporter molecules out of the neuron and into the synapse. Once in the synapse, the high concentrations of dopamine causes feelings of pleasure and euphoria. The excess norepinephrine may be responsible for the alertness and anti-fatigue effects of methamphetamine.

Methamphetamine can also affect the brain in other ways. For example it can cause cerebral edema, brain hemorrhage, paranoia, and hallucinations. Some of methamphetamine's effects on the brain may be long-lasting and even permanent. Research with laboratory animals has demonstrated that exposure to a single, high-dose of methamphetamine or prolonged exposure at low doses destroys up to fifty percent of the dopamine-producing neurons in certain parts of the brain. Studies are currently underway to study the long-term effects of chronic methamphetamine abuse in humans. Although the damage of chronic methamphetamine abuse may not be immediately apparent in humans, scientists believe that the progressive decrease in numbers of dopamine-producing neurons may lead to symptoms of Parkinson's disease.
Methamphetamine also has widespread effects on other parts of the body. It can cause high blood pressure, arrhythmias, chest pain, shortness of breath, nausea, vomiting, and diarrhea. It can also increase body temperature which can be lethal in overdose situations.

Methamphetamine

Methamphetamine is an addictive drug that belongs to a class of drugs known as stimulants. This class also includes cocaine, caffeine, and other drugs. Methamphetamine is made illegally with relatively inexpensive over-the-counter ingredients. Many of the ingredients that are used to produce methamphetamine, such as drain cleaner, battery acid, and antifreeze, are extremely dangerous. The rapid proliferation of "basement" laboratories for the production of methamphetamine has led to a widespread problem in many communities in the U.S.

Methamphetamine has many effects in the brain and body. Short-term effects can include increased wakefulness, increased physical activity, decreased appetite, increased respiration, hyperthermia, irritability, tremors, convulsions, and aggressiveness. Hyperthermia and convulsions can result in death. Single doses of methamphetamine have also been shown to cause damage to nerve terminals in studies with animals. Long-term effects can include addiction, stroke, violent behavior, anxiety, confusion, paranoia, auditory hallucinations, mood disturbances, and delusions. Long-term use can also cause damage to dopamine neurons that persists long after the drug has been discontinued.

Methamphetamine acts on the pleasure circuit in the brain by altering the levels of certain neurotransmitters present in the synapse. Chemically, methamphetamine is closely related to amphetamine, but its effects on the central nervous system are greater than those of amphetamine. Methamphetamine is also chemically similar to dopamine and another neurotransmitter, norepinephrine. It produces its effects by causing dopamine and norepinephrine to be released into the synapse in several areas of the brain, including the nucleus accumbens, prefrontal cortex, and the striatum, a brain area involved in movement. Specifically, methamphetamine enters nerve terminals by passing directly through nerve cell membranes. It is also carried into the nerve terminals by transporter molecules that normally carry dopamine or norepinephrine from the synapse back into the nerve terminal. Once in the nerve terminal, methamphetamine enters dopamine and norepinephrine containing vesicles and causes the release of these neurotransmitters. Enzymes in the cell normally chew up excess dopamine and norepinephrine, however methamphetamine blocks this breakdown. The excess neurotransmitters are then carried by transporter molecules out of the neuron and into the synapse. Once in the synapse, the high concentration of dopamine causes feelings of pleasure and euphoria. The excess norepinephrine may be responsible for the alertness and anti-fatigue effects of methamphetamine.

Methamphetamine can also affect the brain in other ways. For example it can cause cerebral edema, brain hemorrhage, paranoia, and hallucinations. Some of the effects of methamphetamine on the brain may be long-lasting and even permanent. Recent research in humans has shown that even three years after chronic methamphetamine users have discontinued use of the drug there is still a reduction in their ability to transport dopamine back into neurons. This clearly demonstrates that there is a long-lasting impairment in dopamine function as a result of drug use. This is highly significant because dopamine has a major role in many brain functions, including experiences of pleasure, mood, and movement. In these same studies, researchers compared the damage to the dopamine system of methamphetamine users to that seen in patients with Parkinson's disease. Parkinson's disease is characterized by a progressive loss of dopamine neurons in brain regions that are involved in movement. Although the damage to the dopamine system was greater in the Parkinson's patients, the brains of former methamphetamine users showed similar patterns to that seen in Parkinson's disease. Scientists now believe that the damage to the dopamine system from long-term methamphetamine use may lead to

symptoms of Parkinson's disease (It should be noted that Parkinson's disease itself is not caused by drug use.). In support of this, research with laboratory animals has demonstrated that exposure to a single, high-dose of methamphetamine or prolonged exposure at low doses destroys up to fifty percent of the dopamine-producing neurons in certain parts of the brain.

Methamphetamine also has widespread effects on other parts of the body. It can cause high blood pressure, arrhythmias, chest pain, shortness of breath, nausea, vomiting, and diarrhea. It can also increase body temperature which can be lethal in overdose situations.

Marijuana

Marijuana is the dried leaves and flowers of the cannabis plant. Tetrahydrocannabinol (THC) is the main ingredient in marijuana that causes people who use it to experience a calm euphoria. Marijuana changes brain messages that affect sensory perception and coordination. This can causes users to see, hear and feel stimuli differently and to exhibit slower reflexes.

THC, the main active ingredient in marijuana, binds to and activates specific receptors, known as cannabiniod receptors. There are many of these receptors in parts of the brain that control memory, thought, concentration, time and depth perception and coordinated movement.

By activating these receptors, THC interferes with the normal functioning of the cerebellum, the part of the brain most responsible for balance, posture, and coordination of movement. The cerebellum coordinates the muscle movements ordered by the motor cortex. Nerve impulses alert the cerebellum that the motor cortex has directed a part of the body to perform a certain action. Almost instantly, impulses from that part of the body inform the cerebellum as to how the action is being carried out. The cerebellum compares the actual movement with the intended movement and then signals the motor cortex to make any necessary corrections. In this way, the cerebellum ensures that the body moves smoothly and efficiently.

The hippocampus, which is involved with memory formation, also contains many cannabinoid receptors. Studies have suggested that marijuana activates cannabinoid receptors in the hippocampus and affects memory by decreasing the activity of neurons in this area. The effect of marijuana on long-term memory is less certain, but while someone is under the influence of marijuana, short-term memory can be compromised. Further, research studies have shown chronic administration of THC can permanently damage the hippocampus of rats, suggesting that marijuana use can lead to permanent memory impairment.

Marijuana also affects receptors in brain areas and structures responsible for sensory perception. Marijuana interferes with the receiving of sensory messages (for example, touch, sight, hearing, taste, and smell) in the cerebral cortex. Various parts of the body send nerve signals to the thalamus, which then routes these messages to the appropriate areas of the cerebral cortex. An area of the sensory cortex, called the somatosensory cortex, receives messages that it interprets as body sensations such as touch and temperature. The somatosensory cortex lies in the parietal lobe of each hemisphere along the central fissure, which separates the frontal and parietal lobes. Each part of the somatosensory cortex receives and interprets impulses from a specific part of the body. Other specialized areas of the cerebrum receive the sensory impulses related to seeing, hearing, taste, and smell. Impulses from the eyes travel along the optic nerve and then are relayed to the visual cortex in the occipital lobes. Portions of the temporal lobes receive auditory messages from the ears. The area for taste lies buried in the lateral fissure, which separates the frontal and temporal lobes. The center for smell is on the underside of the frontal lobes. Marijuana activates cannabinoid receptors in these various areas of the cerebrum and results in the brain misinterpreting the nerve impulses from the different sense organs.

For many years, it was known that THC acted on cannabinoid receptors in the brain. It was hypothesized that since the normal brain produces these receptors, there must also be a substance produced by the brain itself that acts on these receptors. Despite years of effort, however, the brain's

THC-like substance eluded scientists, and whether or not such a substance existed remained a mystery. Finally, in 1992, scientists discovered a substance produced by the brain that activates the THC receptors and has many of the same physiological effects as THC. The scientists named the substance anandamide, from a Sanskrit word meaning bliss. The discovery of anandamide opened whole new avenues of research. For instance, since the brain produces both anandamide and the cannabinoid receptors to which it binds, it was thought that anandamide must play a role in the normal functioning of the brain. Scientists are now actively investigating anandamide's function in the brain. This research will not only help in gaining a greater understanding of how marijuana acts in the brain and why it is abused, but it will also provide new clues about how the healthy brain works.
The discovery of anandamide may also lead to a greater understanding of certain health problems and ultimately to more effective treatments. When made synthetically and given orally, THC can be used to treat nausea associated with chemotherapy and stimulate appetite in AIDS wasting syndrome. It may also be useful for other conditions, including glaucoma. Now that the brain's own THC-like substance has been identified, researchers may soon be able to uncover the mechanisms underlying the therapeutic effects of THC. This could then lead to the development of more effective and safer treatments for a variety of conditions.

Recent research in animals has also suggested that long-term use of marijuana (THC) produces changes in the limbic system that are similar to those that occur after long-term use of other major drugs of abuse such as cocaine, heroin, and alcohol. These changes are most evident during withdrawal from THC. During withdrawal, there are increases in both the levels of a brain chemical involved in stress and certain emotions and the activity of neurons in the amygdala. These same kinds of changes also occur during withdrawal from other drugs of abuse, suggesting that there may be a common factor in the development of drug dependence.

Opiates

Opiates are powerful drugs derived from the poppy plant that have been used for centuries to relieve pain. They include opium, heroin, morphine, and codeine. Even centuries after their discovery, opiates are still the most effective pain relievers available to physicians for treating pain. Although heroin has no medicinal use, other opiates, such as morphine and codeine, are used in the treatment of pain related to illnesses (for example, cancer) and medical and dental procedures. When used as directed by a physician, opiates are safe and generally do not produce addiction. But opiates also possess very strong reinforcing properties and can quickly trigger addiction when used improperly.

Opiates elicit their powerful effects by activating opiate receptors that are widely distributed throughout the brain and body. Once an opiate reaches the brain, it quickly activates the opiate receptors that are found in many brain regions and produces an effect that correlates with the area of the brain involved. Two important effects produced by opiates, such as morphine, are pleasure (or reward) and pain relief. The brain itself also produces substances known as endorphins that activate the opiate receptors. Research indicates that endorphins are involved in many things, including respiration, nausea, vomiting, pain modulation, and hormonal regulation.

When opiates are prescribed by a physician for the treatment of pain and are taken in the prescribed dosage, they are safe and there is little chance of addiction. However, when opiates are abused and taken in excessive doses, addiction can result. Findings from animal research indicate that, like cocaine and other abused drugs, opiates can also activate the brain's reward system. When a person injects, sniffs, or orally ingests heroin (or morphine), the drug travels quickly to the brain through the bloodstream. Once in the brain, the heroin is rapidly converted to morphine, which then activates opiate receptors located throughout the brain, including within the reward system. (Note: Because of its chemical structure, heroin penetrates the brain more quickly than other opiates, which is probably why many addicts prefer heroin.) Within the reward system, the morphine activates opiate receptors in the VTA, nucleus accumbens, and cerebral cortex. Research suggests that stimulation of opiate receptors by morphine results in feelings of reward and activates the pleasure circuit by causing greater amounts of dopamine to be released within the nucleus accumbens. This causes an intense euphoria, or rush, that lasts only briefly and is followed by a few hours of a relaxed, contented state. This excessive release of dopamine and stimulation of the reward system can lead to addiction.

Opiates also act directly on the respiratory center in the brainstem, where they cause a slowdown in activity. This results in a decrease in breathing rate. Excessive amounts of an opiate, like heroin, can cause the respiratory centers to shut down breathing altogether. When someone overdoses on heroin, it is the action of heroin in the brainstem respiratory centers that can cause the person to stop breathing and die.

As mentioned earlier, the brain itself produces endorphins that have an important role in the relief or modulation of pain. Sometimes, though, particularly when pain is severe, the brain does not produce enough endorphins to provide pain relief. Fortunately, opiates, such as morphine are very powerful pain relieving medications. When used properly under the care of a physician, opiates can relieve severe pain without causing addiction.

Feelings of pain are produced when specialized nerves are activated by trauma to some part of the body, either through injury or illness. These specialized nerves, which are located throughout the body, carry the pain message to the spinal cord. After reaching the spinal cord, the message is relayed to other neurons, some of which carry it to the brain. Opiates help to relieve pain by acting in both the spinal cord and brain. At the level of the spinal cord, opiates interfere with the transmission of the pain messages between neurons and therefore prevent them from reaching the brain. This blockade of pain messages protects a person from experiencing too much pain. This is known as analgesia.

Opiates also act in the brain to help relieve pain, but the way in which they accomplish this is different than in the spinal cord.

There are several areas in the brain that are involved in interpreting pain messages and in subjective responses to pain. These brain regions are what allow a person to know he or she is experiencing pain and that it is unpleasant. Opiates also act in these brain regions, but they don't block the pain messages themselves. Rather, they change the subjective experience of the pain. This is why a person receiving morphine for pain may say that they still feel the pain but that it doesn't bother them anymore.

Although endorphins are not always adequate to relieve pain, they are very important for survival. If an animal or person is injured and needs to escape a harmful situation, it would be difficult to do so while experiencing severe pain. However, endorphins that are released immediately following an injury can provide enough pain relief to allow escape from a harmful situation. Later, when it is safe, the endorphin levels decrease and intense pain may be felt. This also is important for survival. If the endorphins continued to blunt the pain, it would be easy to ignore an injury and then not seek medical care.

There are several types of opiate receptors, including the delta, mu, and kappa receptors. Each of these three receptors is involved in controlling different brain functions. For example, opiates and endorphins are able to block pain signals by binding to the mu receptor site. The powerful new technology of cloning has enabled scientists to copy the genes that make each of these receptors. This in turn is allowing researchers to conduct laboratory studies to better understand how opiates act in the brain and, more specifically, how opiates interact with each opiate receptor to produce their effects. This information may eventually lead to more effective treatments for pain and opiate addiction.

Hallucinogens

Hallucinogens are drugs which cause altered states of perception and feeling and which can produce flashbacks. They include natural substances, such as mescaline and psilocybin that come from plants (cactus and mushrooms), and chemically manufactured ones, such as LSD and MDMA (ecstasy). LSD is manufactured from lysergic acid, which is found in ergot, a fungus that grows on rye and other grains. MDMA is a synthetic mind-altering drug with hallucinogenic properties. Although not a true hallucinogen in the pharmacological sense, PCP causes many of the same effects as hallucinogens and so is often included with this group of drugs. Hallucinogens have powerful mind-altering effects. They can change how the brain perceives time, everyday reality, and the surrounding environment. They affect regions and structures in the brain that are responsible for coordination, thought processes, hearing, and sight. They can cause people who use them to hear voices, see images, and feel sensations that do not exist. Researchers are not certain that brain chemistry permanently changes from hallucinogen use, but some people who use them appear to develop chronic mental disorders. PCP and MDMA are both addicting; whereas LSD, psilocybin, and mescaline are not.

Research has provided many clues about how hallucinogens act in the brain to cause their powerful effects. However, because there are different types of hallucinogens and their effects are so widespread, there is still much that is unknown. The following paragraphs describe some of what is known about this diverse group of drugs.

LSD binds to and activates a specific receptor for the neurotransmitter serotonin. Normally, serotonin binds to and activates its receptors and then is taken back up into the neuron that released it. In contrast, LSD binds very tightly to the serotonin receptor, causing a greater than normal activation of the receptor. Because serotonin has a role in many of the brain's functions, activation of its receptors by LSD produces widespread effects, including rapid emotional swings, and altered perceptions, and if taken in a large enough dose, delusions and visual hallucinations.

MDMA, which is similar in structure to methamphetamine, causes serotonin to be released from neurons in greater amounts than normal. Once released, this serotonin can excessively activate serotonin receptors. Scientists have also shown that MDMA causes excess dopamine to be released from dopamine-containing neurons. Particularly alarming is research in animals that has demonstrated that MDMA can damage and destroy serotonin containing neurons. MDMA can cause hallucinations, confusion, depression, sleep problems, drug craving, severe anxiety, and paranoia.

PCP, which is not a true hallucinogen, can affect many neurotransmitter systems. It interferes with the functioning of the neurotransmitter glutamate, which is found in neurons throughout the brain. Like many other drugs, it also causes dopamine to be released from neurons into the synapse. At low to moderate doses, PCP causes altered perception of body image, but rarely produces visual hallucinations. PCP can also cause effects that mimic the primary symptoms of schizophrenia, such as delusions and mental turmoil. People who use PCP for long periods of time have memory loss and speech difficulties.

Nicotine

Tobacco, which comes primarily from the plant nicotiana tabacum, has been used for centuries. It can be smoked, chewed, or sniffed. The first description of addiction to tobacco is contained in a report from the New World in which Spanish soldiers said that they could not stop smoking.

When nicotine was isolated from tobacco leaves in 1828, scientists began studying its effects in the brain and body. This research eventually showed that, although tobacco contains thousands of chemicals, the main ingredient that acts in the brain and produces addiction is nicotine. More recent research has shown that the addiction produced by nicotine is extremely powerful and is at least as strong as addictions to other drugs such as heroin and cocaine.

Some of the effects of nicotine include changes in respiration and blood pressure, constriction of arteries, and increased alertness. Many of these effects are produced through its action on both the central and peripheral nervous system.

Nicotine readily enters the body. When tobacco is smoked, nicotine enters the bloodstream through the lungs. When it is sniffed or chewed, nicotine passes through the mucous membranes of the mouth or nose to enter the bloodstream. Nicotine can also enter the bloodstream by passing through the skin. Regardless of how nicotine reaches the bloodstream, once there, it is distributed throughout the body and brain where it activates specific types of receptors known as cholinergic receptors.

Cholinergic receptors are present in many brain structures, as well as in muscles, adrenal glands, the heart, and other body organs. These receptors are normally activated by the neurotransmitter acetylcholine, which is produced in the brain, and by neurons in the peripheral nervous system. Acetylcholine and its receptors are involved in many activities, including respiration, maintenance of heart rate, memory, alertness, and muscle movement.

Because the chemical structure of nicotine is similar to that of acetylcholine's, it is also able to activate cholinergic receptors. But unlike acetylcholine, when nicotine enters the brain and activates cholinergic receptors, it can disrupt the normal functioning of the brain.

Regular nicotine use causes changes in both the number of cholinergic receptors and the sensitivity of these receptors to nicotine and acetylcholine. Some of these changes may be responsible for the development of tolerance to nicotine. Once tolerance has developed, a nicotine user must regularly supply the brain with nicotine in order to maintain normal brain functioning. If nicotine levels drop, the nicotine user will begin to feel uncomfortable withdrawal symptoms.

Recently, research has shown that nicotine also stimulates the release of the neurotransmitter dopamine in the brain's pleasure circuit. Using microdialysis, a technique that allows minute quantities of neurotransmitters to be measured in precise brain areas, researchers have discovered that nicotine causes an increase in the release of dopamine in the nucleus accumbens. This release of dopamine is similar to that seen for other drugs of abuse, such as heroin and cocaine, and is thought to underlie the pleasurable sensations experienced by many smokers.

Other research is providing even more clues as to how nicotine may exert its effects in the brain. Cholinergic receptors are relatively large structures that consist of several components known as

subunits. One of these subunits, the ß (beta) subunit, has recently been implicated as having a role in nicotine addiction. Using highly sophisticated bioengineering technologies, scientists were able to produce a new strain of mice in which the gene that produces the ß subunit was missing. Without the gene for the ß subunit, these mice, which are known as "knockout" mice because a particular gene has been knocked out, were unable to produce any ß subunits. What researchers found when they examined these knockout mice was that in contrast to mice who had an intact receptor, mice without the ß subunit would not self- administer nicotine. These studies demonstrate that the ß subunit plays a critical role in mediating the pleasurable effects of nicotine. The results also provide scientists with valuable new information about how nicotine acts in the brain, information that may eventually lead to better treatments for nicotine addiction.

However nicotine may not be the only psychoactive ingredient in tobacco. Using advanced brain imaging technology, it is possible to actually see what tobacco smoking is doing to the brain of an awake and behaving human being. Using one type of brain imaging, positron emission tomography (PET), scientists discovered that cigarette smoking causes a dramatic decrease in the levels of an important enzyme that breaks down dopamine.

The decrease in this enzyme, known as monoamine-oxidase-A (MAO-A), results in an increase in dopamine levels. Importantly, this particular effect is not caused by nicotine but by some additional, unknown compound in cigarette smoke. Nicotine itself does not alter MAO-A levels; it affects dopamine through other mechanisms. Thus, there may be multiple routes by which smoking alters the neurotransmitter dopamine to ultimately produce feelings of pleasure and reward.

That nicotine is a highly addictive drug can clearly be seen when one considers the vast number of people who continue to use tobacco products despite their well known harmful and even lethal effects. In fact, at least 90% of smokers would like to quit, but each year fewer than 10% who try are actually successful. But, while nicotine may produce addiction to tobacco products, it is the thousands of other chemicals in tobacco that are responsible for its many adverse health effects.

Smoking either cigarettes or cigars can cause respiratory problems, lung cancer, emphysema, heart problems, and peripheral vascular disease. In fact, smoking is the largest preventable cause of premature death and disability. Cigarette smoking kills at least 400,000 people in the United States each year and makes countless others ill, including those who are exposed to secondhand smoke. The use of smokeless tobacco is also associated with serious health problems.

Chewing tobacco can cause cancers of the oral cavity, pharynx, larynx, and esophagus. It also causes damage to gums that may lead to the loss of teeth. Although popular among sports figures, smokeless tobacco can also reduce physical performance.